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Investigating the Anticancer Effect of Compound Honey Syrup Herbal Product on Gastric Adenocarcinoma Cells

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Abstract:
Introduction: Apoptosis has provided solutions for effective anticancer treatments, and today one of the most interesting strategies is drug interventions that can mediate the death of cancer cells through the induction of apoptosis. Many plant compounds are known to have anti-tumor activity in this way. Compound Honey Syrup is used in Iranian traditional medicine and its cytotoxicity has been determined on melanoma cells. The purpose of this research was to investigate the anticancer effect of Compound Honey Syrup herbal product on gastric adenocarcinoma cells and the mechanism of this effect.
Method: The lethal effect of Compound Honey Syrup on gastric adenocarcinoma (AGS) and fibroblastic (HgF) cells after 24 hours of incubation was investigated by MTT calorimetric method. Annexin FITC-V and PI staining

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method determined apoptotic cell death. The change in the activity of caspases 8 and 9 was also evaluated by enzymatic method. The base membrane of the model was used to evaluate the invasion ability of Compound Honey Syrup cancer cells.
Results: Compound Honey Syrup had a strong and concentration-dependent killing effect on AGS cells and caused cell death mainly by inducing early apoptosis. The increased activity of caspases 8 and 9 was involved in this process. Compound Honey Syrup also reduced the ability of cancer cells to invade.
Conclusion: By activating caspases 8 and 9, COMPOUND HONEY SYRUP led to the apoptotic death of human gastric cancer cells. In addition, COMPOUND HONEY SYRUP can be an effective factor for investigating the prevention or treatment of stomach cancer in humans by reducing the strength and invasion of cancer cells.
Keywords: cancer, herbal product COMPOUND HONEY SYRUP, apoptosis, caspase

Introduction

Cancer is the leading cause of death among men and women. Today, many treatment methods are used to treat cancers, but unfortunately, in most cases, the response to the treatment is very weak and it is often associated with adverse side effects. Therefore, research to produce drugs with more efficiency and less toxicity is necessary. Many herbal compounds with various biological effects are known, which are considered as anticancer drugs in modern pharmaceutical science (1,2).

The morphological characteristics of the cell apoptosis process include the reduction of cell volume, the condensation of peripheral heterochromatin, the shrinkage of the cytoplasm, the blebbing of the plasma membrane, and the phagocytosis of spherical cytoplasmic bodies fragmented by macrophages or other phagocytic cells. Since apoptosis in one cell does not induce death in adjacent cells, inflammation or tissue damage does not occur (3). Maintaining homeostasis in normal mammalian tissues is due to the balance between proliferation and cell death through apoptosis. In most cases, apoptosis is inhibited or disturbed in tumors, and as a result, the rate of cell proliferation is very high (4). Malignant transformation processes of cancer progression and metastasis result from alterations in normal apoptotic pathways. Apoptosis occurs in most tumor cells through two main signal transmission pathways. The external pathway starts with the activation of death receptors and the internal pathway starts with the release of apoptogenic factors from the mitochondria to the cytoplasm. Following these two, a cascade of molecules is activated, which eventually leads to the apoptotic death of cells by activating proteolytic caspases (7-5). Caspases, which are cysteine-dependent aspartate-specific proteases, play a key role in causing apoptosis. Therefore, their specific inhibitors can prevent apoptosis (8,9).

Apoptosis has provided solutions for effective anticancer therapy, and so far many compounds have been reported to have anticancer effects through apoptosis induction (10). Therefore, nowadays, one of the interesting strategies that have been considered in cancer chemotherapy is drug interventions that can mediate the death of malignant cells through the induction of apoptosis (11). There are many compounds in medicinal and edible plants that induce their antitumor activity by inducing apoptosis in cancer cells (12,13). Tumor growth and metastasis requires angiogenesis or the formation of new blood vessels and the ability to invade and capture new tissues by invasive cancer cells, and controlling angiogenesis and the ability to invade cancer cells can be an anti-tumor strategy. Nowadays, the studies of many scientists have been drawn towards the use of plant compounds as angiogenesis inhibitors and the ability of cell invasion as anti-tumor strategies (18-14). Nowadays, the use of complementary medicine in the treatment of various diseases, especially chronic diseases, has become popular. Honey is one of the most widely used drugs in complementary medicine. Honey, which is one of the components of compound mead syrup, contains the flavonoid components of quercetin, kaempferol, apigenin and genistein (19) and phenolic components, and this group of flavonoids in honey is also considered as a pharmacological stimulator of CFTR (20). One hypothesis is that honey, due to the abundance of polyphenolic flavonoids, leads to the inhibition of P-glycoprotein, which is one of the transfer proteins in multi-drug resistance (MDR) organisms (21). Cardamom, cinnamon, dogwood and ginger, which are among the components of compound honey syrup, have kaempferol and quercetin flavonoids (23). Many compounds are known to target cancer cells, but the success of these compounds as an anticancer compound largely depends on their ability to activate pathways that cause the death of cancer cells by stopping the cell cycle (Cell Cycle Arrest) and inducing Apoptosis is caused and they can prevent tumor metastasis by reducing the ability of cancer cells to invade (24) in order to discover new herbal anticancer drugs, in this study we tried to determine the

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effect of the new anticancer compound HONEY SYRUP on the growth and proliferation of human gastric cancer cells (AGS).) and normal human fibroblastic cells (HF). Also, in order to investigate the efficiency of this compound and determine its anticancer mechanism, cell cycle arrest, the type of induced cell death (apoptosis or necrosis) and the ability of cell invasion in gastric cancer cells were investigated.

Materials and Methods

Preparation of herbal product COMPOUND HONEY SYRUP

In order to prepare the medicine, high-quality natural honey was obtained from a reputable center in Sabzevar, and the desired drugs, including cinnamon, ginger, saffron, cardamom, and kholanjan, were obtained from the Iranian medicinal plant market, and after identification and physicochemical quality control tests, according to valid herbal pharmacopoeias, including correct identification Plant, total ash, ash insoluble in acid and microbial tests were used in the preparation of medicine and finally the tests of appearance characteristics, pH, density, viscosity, dry weight of the extract, microbial and fungal control were performed on the final product.

•There are 2grams of cinnamon, 2grams of cardamom, 1gram of ginger, 1gram of kholanjan and 1gram of saffron in every 100cc of mixed honey syrup.

Cell culture

Gastric adenocarcinoma cell line (AGS) and human gingival fibroblast (HF) were cultured in DMEM culture medium enriched with %10FCS, 100U/ml penicillin and 100µg/ml streptomycin to perform various tests of cells by trypsin 0solution. %0.25- %0.1EDTA was separated and after washing, the percentage of cell viability was determined using trypan blue by a hemocytometer. Cells with a viability percentage higher than 90were used to perform the tests.

Measurement of Cell Growth and Proliferation

In order to investigate the effect of herbal product COMPOUND HONEY SYRUP on cell growth and proliferation by MTT colorimetric method (24), 2x 104gastric adenocarcinoma (AGS) or fibroblastic (HgF) cells were poured into each well of a 96-well microplate. And they were treated with different concentrations of COMPOUND HONEY SYRUP plant product (4000-250µg/ml) for 24hours. Minimum wells were assigned for each concentration. Three wells were also examined as control without drug. After 24hours of incubation, 25microliters of MTT solution (mg/ml) was added to each well and the plate was incubated for another 3hours. Then dimethyl sulfoxide (DMSO) was added to each well. Optical absorption was read by an ELISA reader at a wavelength of 545 nm against blank (DMSO).

Examination of Cell Apoptosis and Necrosis

A number of 5x 105HgF cancer cells were poured into each well of a 6-well plate and treated with different concentrations of COMPOUND HONEY SYRUP (4000-500µg/ml). After 24hours of incubation, the cells were incubated with FITC-conjugated Annexin V (FITC-V Annexin) and propidium iodide PI and analyzed by flow cytometry. FITC V-positive and PI-negative cell populations were considered as primary apoptosis, FITC-V-positive and PI-positive cell populations were considered as secondary apoptosis or post-apoptotic necrosis, and FITC-V-negative and PI-positive cell populations were considered as necrosis.

Evaluation of the Invasion Ability of Gastric Cancer Cells

In this research, the Boyden Chamber Assay method was used to investigate migration and cell invasion and escape, in which the invasion of cancer cells is through the basement membrane (ECMatrix) model (25,26). For this purpose, 1x 105AGS cells were added to the upper cavity of the well along with DMEM culture medium without absorbent material (FBS) in the control and test groups treated with different concentrations of COMPOUND HONEY SYRUP (2000-250micrograms/ml). Culture medium containing %10FBS was added to the bottom cavity of each well and the plate was incubated for 24hours. Cancer cells that had the ability to invade passed through the membrane and were lysed by separating buffer from the membrane and finally tracked by the green fluorescent dye CyQuant GR (Molecular Probes) that binds to cellular nucleic acids. After excitation at a wavelength of 480nm, the

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emitted light was read by a fluorescent plate reader system at a wavelength of 520nm. The light intensity obtained was proportional to the number of cells that passed through the membrane of the invading cells.

Measuring the Activity of Caspases 8 and 9 in AGS Cancer Cells

In order to quantitatively evaluate apoptosis, the enzymatic activity of caspases 8and 9was done using colorimetric methods. The number of 2x 106AGS cells in each well was incubated for 24hours in the test group (concentration of 1500µg/ml of COMPOUND HONEY SYRUP) and the control group. After cell lysis, the extracted cytosolic proteins were incubated with the reaction buffer and caspase 8substrate (IETD-pNA) or caspase 9substrate (LEHD-pNA) and the optical absorbance of the obtained color was read at 405nm wavelength. An increase in the activity of caspases was reported by comparing the results of the test group with the untreated control group.

Statistical analysis of the Obtained Results

In order to compare the results, SPSS 21statistical software and ANOVA statistical test were used. The minimum level of significance was $p<0.05$.

Results:

The effect of different concentrations of COMPOUND HONEY SYRUP product on the rate of cell growth and proliferation:

The results of the effect of COMPOUND HONEY SYRUP product on the growth and proliferation of human gastric adenocarcinoma cells (AGS) and human gingival fibroblast cells (HgF) were reported as the average of three independent experiments (Chart 1). Different concentrations of COMPOUND HONEY SYRUP product growth and proliferation of cells they reduced gastric adenocarcinoma, while the rate of inhibiting the growth and proliferation of fibroblastic cells was lower (Chart 1).

Apoptosis Induction in Cancer Cells Treated with COMPOUND HONEY SYRUP Product

In the cells of the control group (untreated), %1necrosis and %3primary apoptosis were observed. The percentage of induction of necrosis, primary apoptosis and secondary apoptosis in AGS cells 1, 3and 0, respectively, by the concentration of 1500; 1, 76and 1by the concentration of 2000, 8, 67and 4by the concentration of 2500; 14, 67 and 4by the concentration of 3000and 72, 3and %5by the concentration of 4000µg/ml COMPOUND HONEY SYRUP (Chart 2).

Evaluation of the Invasion Ability of Cancer Cells Treated with COMPOUND HONEY SYRUP

COMPOUND HONEY SYRUP dose-dependently inhibited the invasion of AGS cells in vitro without having strong toxicity on them at these concentrations. In this method, the number of AGS cells passing through the base membrane of the model (invader) was proportional to the obtained light intensity (Chart 3).

Activation of Caspases 8 and 9 in the Pathway of Apoptosis Induction by COMPOUND HONEY SYRUP

The obtained results showed a time-dependent increase in the proteolytic activity of caspases 8and 9in cells treated with COMPOUND HONEY SYRUP product compared to their activity in the control group (Chart 4,5).

Discussion:

In general, herbal remedies are commonly used to treat ailments and various disease symptoms such as fever, inflammation, and pain without sufficient information about their mechanism of action. Considering the fact that cancer is the biggest cause of death among men and women, it is necessary to research and produce anticancer drugs with greater efficiency and less toxicity. The effectiveness of many compounds obtained from plants in the prevention or treatment of cancer in cancer cells cultivated in the laboratory and also in some laboratory models has been determined (25).

Honey, which is one of the components of compound mead syrup, contains the flavonoid components quercetin, kaempferol, apigenin and genistein (26) and phenolic components, and this group of flavonoids in honey are also considered pharmacological stimulators of CFTR. One hypothesis is that honey, due to the abundance of polyphenolic flavonoids, leads to the inhibition of P-glycoprotein, which is one of the transfer proteins in multi-drug resistance (MDR) organisms (27).

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In order to investigate the effect of herbal product COMPOUND HONEY SYRUP on gastric cancer, first its effect on the growth and proliferation of human gastric adenocarcinoma (AGS) cancer cell line cultured in the laboratory was investigated by MTT test. Different concentrations of COMPOUND HONEY SYRUP caused strong and concentration-dependent inhibition of the growth and proliferation of gastric cancer cells (AGS). Cell growth inhibition by the lowest concentration was 43 ± %0.6 and reached 92 ± %0.4 by the highest concentration. While this level of toxicity on normal human fibroblast cells (HF) was 0.7±9 and %0.6±42. These results showed that the herbal product COMPOUND HONEY SYRUP had a significant killing effect on stomach cancer cells. Also, COMPOUND HONEY SYRUP selectively destroyed gastric cancer cells compared to HgF normal cells, and its toxicity level on normal cells was acceptable and much lower than cancer cells. In this research, COMPOUND HONEY SYRUP selectively destroyed AGS cancer cells compared to HgF normal cells, but the inhibition percentage (cytotoxicity rate) of SK-MEL melanoma cells after 24 hours of incubation with a concentration of 5000 µg/ml of COMPOUND HONEY SYRUP was only %47, which was much lower than the lethal effect of COMPOUND HONEY SYRUP on gastric cancer cells (AGS).

Many compounds have been identified that have a lethal effect on cancer cells, but their use as useful anticancer compounds depends on their ability to activate apoptotic pathways in cancer cells (28). Therefore, in this study, the type of induced cell death (apoptosis or necrosis) in human gastric adenocarcinoma (AGS) cells treated with COMPOUND HONEY SYRUP was investigated by flow cytometry technique. All investigated concentrations of COMPOUND HONEY SYRUP induced primary apoptosis, secondary apoptosis and necrosis in gastric cancer cells, but the primary apoptosis induction rate was much higher. COMPOUND HONEY SYRUP in concentrations less than 2,500 µg/ml reduced the growth and proliferation of gastric cancer cells mainly through primary apoptotic mechanisms, the amount of cell necrosis increased at a concentration of 3,000 µg/ml, but still the main cell killing mechanism was secondary apoptosis A high concentration of 4000 µg/ml of COMPOUND HONEY SYRUP killed AGS cancer cells mainly by inducing cell necrosis. Therefore, apoptosis plays an important role in the anti-cancer property of COMPOUND HONEY SYRUP product, especially in concentrations less than 3000 µg/ml (1,29,30).

In order to identify the mechanism of apoptosis induction by COMPOUND HONEY SYRUP, the level of activity of caspase 8 and 9 in AGS cancer cells was investigated and it was found that COMPOUND HONEY SYRUP increases the activity of both caspase 8 and 9, but the increase in caspase 9 activity was much higher. Therefore, the mitochondrial pathway of apoptosis has a greater role in killing cells (31-33,1).

Antioxidants are substances that are able to deal with the effects of the physiological process of oxidation in tissues. There is overwhelming evidence supporting the nutritional effects of artificial antioxidants added to foods such as butylhydroxyanisole, butylhydroxytoluene, and tert-beta-hydroxyquinone. In addition, the risk of liver damage and cancer in laboratory animals is one of the disadvantages of using artificial antioxidants (8-5). Therefore, the need for strong antioxidants with less toxicity and greater effectiveness is an inevitable necessity. Antioxidants in honey include glucose oxidase, catalase, ascorbic acid, phenolic acids, flavonoids, amino acids and proteins. It seems that the most important antioxidants in honey are phenols (15,19,34). Patients who visit therapeutic experts don't continuously report their past restorative history, either because they don't consider it imperative or since they don't consider it important to their issue. technological advancements have demonstrated their potential in enhancing human health and augmenting our medical infrastructure (35,36). Satisfactory therapeutic preparing and taking a point by point therapeutic history, which ought to incorporate the patient's past therapeutic and sedate history and checking the common wellbeing status, are fundamental to distinguish patients with related therapeutic conditions and anticipate the coming about dangers in choosing treatment (37,13). Too, in patients who are making their to begin with visit, pros ought to be counseled to examine different perspectives of their wellbeing status (38,15).Their simplification, counting those that are vague to the specialist, ought to be clarified after checking on the records or conducting a physical examination (39). Just as the issue of health and treatment has a certain complexity, its quality management is also complex and difficult.

After observing the appropriate and safe anticancer effect of COMPOUND HONEY SYRUP on gastric cancer cells and also identifying the induction of apoptosis as an effective mechanism in this effect, the effect of the herbal product COMPOUND HONEY SYRUP on the ability of AGS cells to invade in vitro as a symbol of the antimetastatic effect It was examined in the body. The number of cells passing through the base membrane of the

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model decreased in a concentration-dependent manner by increasing the concentration of COMPOUND HONEY SYRUP, so that the high concentration of COMPOUND HONEY SYRUP completely inhibited the passage of invasive cancer cells.

Conclusion

In general, the results of this research showed that the herbal product COMPOUND HONEY SYRUP has strong, effective and safe anti-cancer properties and can be studied as a possible anti-cancer compound with low risk or safety in cancer mouse models in vivo. be placed

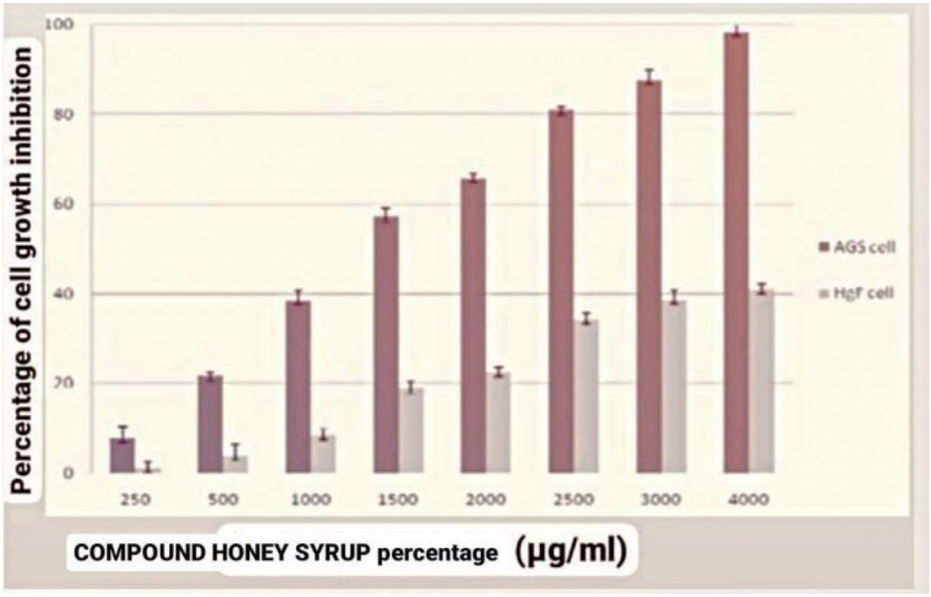

Figure1 : The effect of different concentrations of COMPOUND HONEY SYRUP product on the induction of apoptosis in gastric adenocarcinoma cells (AGS) and human gingival fibroblast cells.

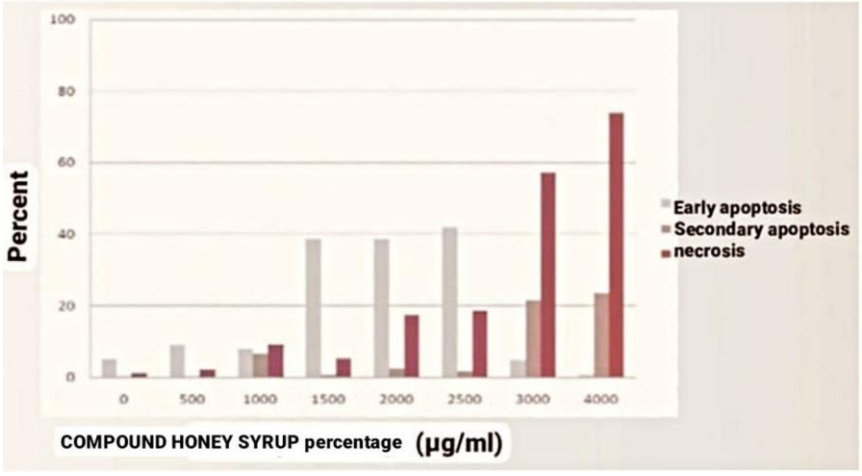

Figure 2: The effect of different concentrations of COMPOUND HONEY SYRUP product on the induction of apoptosis in gastric adenocarcinoma (AGS) cells.

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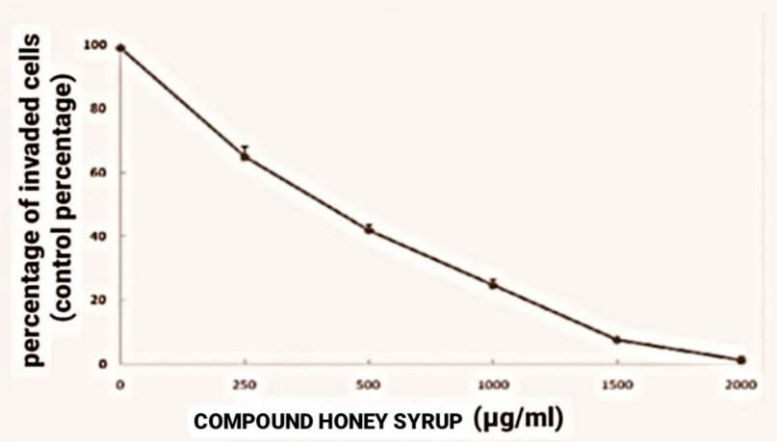

Figure3 : The effect of different concentrations of COMPOUND HONEY SYRUP product on the invasion of gastric adenocarcinoma (AGS) cells.

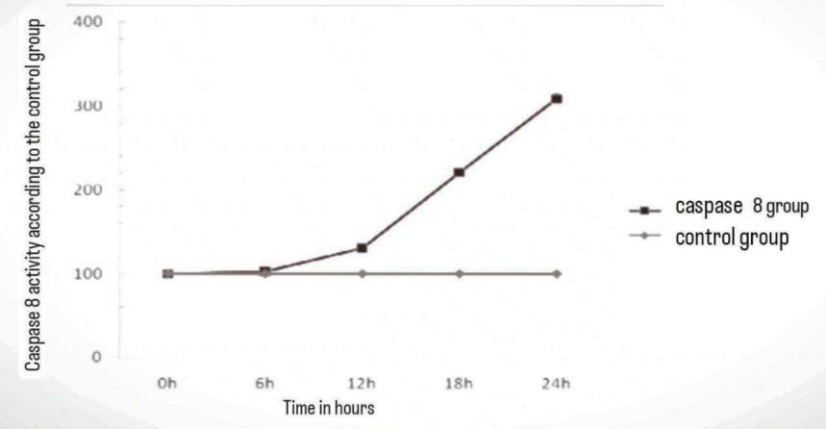

Figure 4: Time-dependent activation of caspase 8 activity in treated gastric adenocarcinoma (AGS) cells.

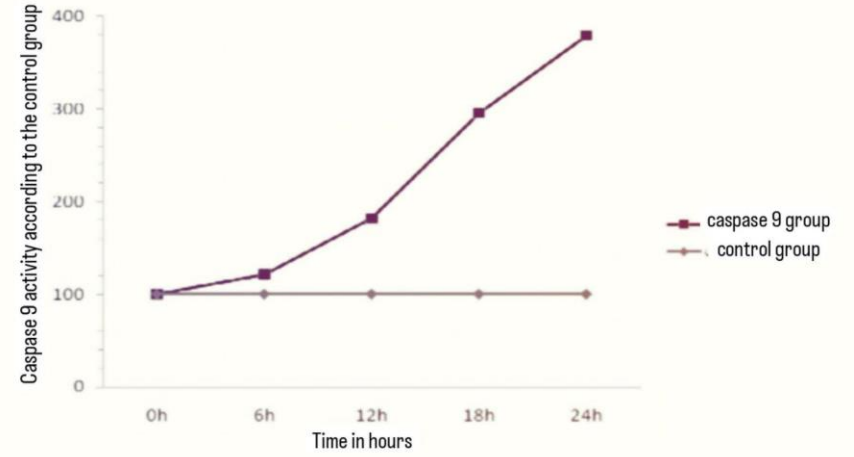

Figure 5: Time-dependent activation of caspase 9 activity in treated gastric adenocarcinoma (AGS) cells.

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